Curing Hematological Diseases

Grant Award Details

Curing Hematological Diseases

Grant Type: Early Translational I

Grant Number: TR1-01273

Project Objective: To establish a robust preclinical model for developing a treatment of patients with FANCA and X-SCID

Investigator:

Name:	Inder Verma
Institution:	Salk Institute for Biological Studies
Type:	PI

Disease Focus: Blood Disorders, Immune Disease

Human Stem Cell Use: iPS Cell

Cell Line Generation: iPS Cell

Award Value: $5,979,252

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Reporting Period: NCE

View Report

Grant Application Details

Application Title: Curing Hematological Diseases

Public Abstract: The primary aim of this project is to develop treatments for incurable diseases of the blood and immune system. X-linked Severe Combined Immunodeficiency (X-SCID) and Fanconi anemia (FA) are two blood diseases where mutations in a single gene results in the disease. XSCID, more commonly known as the “bubble boy” disease, is characterized by a complete failure of the immune system, and typically results in early childhood fatality. The most common treatment for X-SCID is bone marrow transplant using a matched sibling donor. Unfortunately, the lack of suitable donors limits the application of this treatment. In 2000, the first gene therapy "success" resulted in X-SCID patients with a functional immune system. These trials were stopped when it was discovered that several patients in one trial had developed lymphoma, a blood related cancer resulting from unintended consequences of the therapy. FA is a disease where the stability of the genome is compromised and results in premature cell death and lethal anemia. Gene therapy trials for such patients have been largely unsuccessful due to the inability to culture the cells long enough for the correction of the gene. Like XSCID there is a shortage of suitable bone marrow donors for patients, thus development of treatments via other methods is warranted.

From this study and others we have learned 1) gene therapy can work to cure certain diseases, 2) adequate safeguards must be developed to prevent unintended cancer formation, and 3) we need better sources of matched cells and tissues to avoid the problems of rejection.

Our proposal will be using one of the most exciting new developments in regenerative medicine, that is the ability to reprogram a patient's skin, or even hair follicle back to an induced pluripotent stem (iPS) cell, which is similar to embryonic stem cells, without involving embryo destruction. The iPS cell is a good candidate for repair of the specific genetic defects that cause diseases like X-SCID and FA. The reprogrammed, genetically corrected cells are a perfect match for transplantation therapy since they come from the patient. At this stage the corrected cells will be augmented with additional safety factors that work to avoid the downstream potential for cancer. These safe and genetically corrected cells will then be coaxed back into the cells that form the blood and immune systems and used for transplant therapy.

In this work we will be using mouse models that mimic the human diseases of X-SCID and FA and are amenable to treatment with human hematopoietic stem cells. We will be working with human patient and disease-specific cells to demonstrate the feasibility and evaluate the safety in a pre-clinical setting to advance these pioneering new techniques that combine the latest developments in regenerative medicine and gene therapy. Our proposed work will also benefit the successful stem cell based therapies for many other diseases like Parkinson's and diabetes.

Statement of Benefit to California:	The idea that embryonic stem cells (ES cells) have the ability to differentiate into a variety of cell types, tissues, and organs, opens the possibility of tissue engineering, replacement, and cell transplant therapies to cure diseases ranging from Parkinson's, Alzheimer's, diabetes, blood disorders and a host of other debilitating disorders. Rarely comes along a new technology that has the potential to make such a major impact on human health. Recently researchers have discovered methods to reprogram adult fibroblasts and skin cells back into a cell referred to as induced pluripotent stem cell (iPS) that appears to be indistinguishable from the pluripotent ES cell. This is accomplished without the need for embryo destruction and offers great potential to alleviate the problems of immune rejection in cell or tissue transplantation by allowing a patient's own cells to be reprogrammed, expanded then used in therapeutic applications. The principle aim of this proposal is to develop new technologies that can be used to treat two specific devastating hematological disorders X-linked Severe Combined Immunodeficiency (X-SCID) and Fanconi Anemia (FA). Both are rare genetic diseases, and both have devastating effects on the immune and blood systems. The successful development of therapies for these diseases will have an obvious and direct effect on the patients and their families affected by these diseases. From a broader perspective, the establishment of these regenerative medicine techniques has the potential to treat a vast array of disease like Parkinson's, Alzheimer's, diabetes and other blood disorders like thalassemia, Sickle cell anemia, and hemophilia. These diseases all have devastating effects on the patients afflicted, but they also place a tremendous burden on the State in terms of health care cost. Ever more, we need to spend state resources wisely and finding ways to reduce the continually increasing cost of long-term medical care is critical. The work proposed here seeks to do just that by creating outright cures for diseases that if left untreated require substantial and prolonged medical expenditures and incredible suffering for the patients and their families. In other regards keeping the state of California at the forefront of medical breakthroughs and strengthening our biomedical and biotechnology industries. We are a leading force in these fields, not only across the nation but also worldwide.